

2011

Nerve

Neurone (nerve cell) is the structural unit of the nervous system.

Composed of Soma: cell body of the neurone.

② Dendrites Antennas processes receiving signals from other neurones

③ Axon (nerve fibre) Single long process sending impulses away of neurone.

a Myelinated nerve fibres: Myelin sheath is a phn-lipid complex.

It is an insulator -- ion flow 5000 fold interrupted at nodes of Rannvier

It is made by Schwanns cells.

Two types: A fibres (α, β, γ and δ) & B fibres (pregang. autonomic)

b Unmyelinated nerve fibres (C fibres) $< 1 \mu$ in diameter

Surrounded by inactive Schwanns cells (Postgang autonomic)

Nerve and muscle cells have 2 properties: Excitability & Conductivity

Excitability A property of living cells.

* It is the ability of living cells to respond to an adequate stimulus

* Stimulus ^{sudden} changes or events which excite an organism $\rightarrow$ responses

* In nerves, electrical stimuli are preferred over mechanical, chemical or thermal.

● Similar to natural stimuli. ● Don't damage tissues.

● Can be controlled. ● Can be accurately measured.

When the electrical stimulator is turned on, current enters the nerve

at the +ve pole (cathode which is the important element) and leaves at -ve pole

Factors affecting effectiveness of electrical stimulus

(نظري)

① Rate of rise of stimulus intensity.

- Rapid increase in stimulus intensity to threshold value gives active response

- Slowly increased intensity lead to nerve accomodation (see page 7).

② Strength of the stimulus ③ Duration of the stimulus 2 & 3 are intimate

Strength-Duration Curve:

(نظري)

The strength is plotted against minimal time needed to excite



①

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Nerve

- * Within limits, the stronger the stimulus, the shorter the time needed to excite.
- * Rheobase: is the threshold or minimal current needed to give response
- * Utilization time is the time needed by rheobase (R)
- Subthreshold (subminimal) stimuli give local response.
- * T: is the minimal time below which no excitation whatever the strength
- * Chronaxie is the time needed by double rheobase to excite.
- The shorter the chronaxie, the higher the excitability.
- Chronaxie is a measure of excitability.

Measuring the membrane potential: 2 microelectrodes, one inside the nerve and the other inside connected to electric amplifier and very sensitive voltmeter e.g Cathode ray oscilloscope.

Forms of membrane potential in nerve: Resting membrane potential and on stimulation of nerve by threshold stimulus $\rightarrow$ Action potential
Subthreshold stimuli give rise to localised (electronic) potentials

Resting membrane potential (RMP) = Polarised state

- Definition Potential of membrane during rest (inside -ve to outside)
- RMP is found in almost all cells but most marked in nerve & muscle cells
- In large nerve & skeletal muscle fibres RMP = -90 mV in medium sized neurone -70 mV in non excitable cells e.g RBCs & epith. cells RMP = -20 to -40 mV

Causes of RMP

- Selective permeability Passive K^+ contributes to -86 mV i.e 95%
- * Ions inside nerve More Potassium (35 times), Cl^- & PO_4^{3-} outside nerve More Sodium (10 times), Cl^- & HCO_3^-
- * Channels Inward rectifier K^+ channels is 20-100 times more permeable to K^+ (K^+ outflow) than other channels of Na^+ & Ca^{2+} & other ions
- * Net effect Movements of more Potassium from inside to outside of nerve $\rightarrow$ more +ve ions on outside & more -ve ions on inside of nerve

Calculation of RMP

a) Nernst equation : Calculate equilibrium potential (E) for ONE ion

$$E \text{ (millivolt)} = \pm 61 \log \frac{\text{conc. of ion inside}}{\text{conc. of ion outside}}$$

$$E \text{ for } K^{+ve} = -61 \log 35 = -94 \text{ mV}$$

$$E \text{ for } Na^{+ve} = -61 \log \frac{1}{10} = +61 \text{ mV}$$

Conclusion : Polarised state is caused mainly by Potassium ions

b) Goldman equation Considers All ions and Permeability.

Conclusion Selective permeability contributes to -86 mV (93% of RMP)

$Na^+ - K^+$ pump Active Contributes to -4 mV i.e 7% of RMP

* Na^+ ions are pumped out against concentration & electrical gradients

* K^+ ions are pumped in against concentration gradient

* $Na^+ - K^+$ pump ptn is a carrier ptn on cell membrane with 3 characters.

1. It has 3 binding sites on its inside for Na^+ ions.

2. It has 2 binding sites on its outside for K^+ ions.

3. Its inner part has ATPase activity.

Mechanism : When all binding sites are saturated, ATPase is activated and energy is liberated $\rightarrow$ conformation changes in the carrier ptn pumping Na^+ outside & K^+ inside.

Functions : 1. It keeps Na^+ ions outside & K^+ ions inside.

2. It accumulates more +ve charges on outside i.e RMP ; being electrogenic pump.

Voltage gated Na^+ channels | Voltage gated K^+ channels

② outer & inner Gates ① inner gates.

Outer activated gate

Inner Inactivated.

Only outer gates closed During RMP Inner gates are closed

Open

Depolarization

Some open

Closed

Repolarization

All open

②

سنة كسبية
Action potential = nerve impulse = nerve signal

• Definition: series of rapid changes in membrane potential (Dep + Rep) caused by stim. of n. fibre by adequate stimulus.
• results from sequential change in mem. conductance for Na^+ & K^+

• Recording 2 microelectrodes connected to electric amplifier and CRO.

• Description i.e. phases and shape of monophasic A. potential:

1. Stimulus artifact: Indicates time of application of the stimulus

It is caused by current leakage from the electrical stimulus

2. Latent period represents time taken by AP to reach recording electrodes

It depends on 1. Distance between the stimulus & recording electrodes

2. Velocity of action potential.

N.B. Provided LP 2 msec & distance 4 cm, the velocity $\frac{4 \text{ cm}}{2 \text{ msec}} = 20 \text{ m/sec}$.

3. Ascending limb i.e. Depolarization

- Starts slowly i.e. between -90 to -65 mV (firing level)

- Becomes rapid after firing level. It overshoots 0 potential (0 mV) and stops when it reaches +35 mV (reversal of polarity)

4. Descending limb i.e. Repolarization

- Starts rapidly until 70% of repolarization is completed.

- Then slowly until it reaches RMP

5. Hyperpolarization small & prolonged overshoot then gradual return to the RMP. During hyperpol, membrane is more -ve than RMP.

• Duration Spike potential i.e. sharp rise & rapid fall lasts 2 msec.

Hyperpolarization lasts 35 - 40 msec.

• Ionic basis of AP

1. Depol. is caused by Na^+ inflow (influx) viz voltage gated Na^+ channels. They have 2 gates outer activation gate & inner inactivation gate.

2. Repol is caused by K^+ outflow (efflux) viz voltage gated K^+ channels. They have only one activation gate on its inner side. (3)

Gates move in a sequential manner essential for production of A.P.

- a Outer activating Na^+ gates open $\rightarrow$ activation of Na^+ channels $\rightarrow$ depol.
- b Inner inactivating Na^+ gates close $\rightarrow$ inactivation of Na^+ channels.
- c K^+ gates open $\rightarrow$ activation of K^+ channels $\rightarrow$ repolariz.

1) During Depolarization

- a Slow stage from -90 mV to -65 mV [Some] Na^+ channels are opened.
Stimulus $\rightarrow$ initial depol $\rightarrow$ open some Na^+ channels $\rightarrow$ more depol
+ve feed back $\rightarrow$ open more Na^+ channels & so on
- b Rapid stage from -65 to +35 mV [All] Na^+ channels are opened
At +35 mV, inner inactivation Na^+ gate close and remain in this state for few milliseconds before returning to the resting state.

2) During Repolarization Inactivation of Na^+ channels. Activation of K^+ channels.

3) During Hyperpolarization Slow closure of K^+ channels i.e. some are opened

* Notes During RMP, both voltage gated Na^+ and K^+ channels are closed.
 Na^+ channels by outer gates & K^+ channels by inner gate

* During depol. Na^+ channels are more voltage sensitive than K^+ channels i.e. activated at more -ve potential and opening of K^+ channels is slower & more prolonged $\rightarrow$ ++ K^+ conductance comes after ++ Na^+ conductance. However, during depol, both Na^+ and K^+ channels are opened.

* Only during hyperpol: Inward rectifier K^+ channels (non gated) drive mem. potential to RMP i.e. K^+ ions moves inward (so it is called inward).

* During action potential, there is reversal of polarity and not reversal of concent. of Na^+ or K^+ . After A.p. potential, Na^+ & K^+ gradients are reestablished by Na^+ - K^+ pump.
Action potential of a single nerve fibre obeys All or none law which states:
Provided all conditions are constant, action potential once produced, it is of maximal amplitude & conduct maximally regardless the stimulus producing it.

• Biphasic action potential

- Recorded when the 2 electrodes are placed on the outer surface of nerve
- Description
 - 1 At rest, no potential differences between 2 electrodes
 - 2 When depol. reaches 1st electrode, this electrode is -ve relative to other
 - 3 When depol. wave passes the position of nerve between 2 electrodes, potential 0.
 - 4 When depol. reaches 2nd electrode, the 1st electrode is +ve relative to this electrode and the oscilloscope records in the opposite direction.
 - 5 When impulse leaves the 2nd electrode, no potential difference is recorded.

Note If the nerve is crushed between 2 surface electrode $\rightarrow$ monophasic A. poten.

• Compound action potential Action potential in nerve trunk

- It has many peaks because each fibre in the nerve trunk varies in: threshold of stim., thickness, myelin, speed of conduction and distance from the stimulating electrode.
- It is graded (no all or none law)
 - Subthreshold stimuli : no response occurs
 - Threshold stimulus : only low threshold nerve fibres respond
 - ++ intensity of, from threshold to maximal stimulus : Action potential grow in amplitude.
 - Supramaximal stimuli : no further increase in amplitude of A. poten.

Electronic potential and local response : Effect of subthreshold stimulus

These graded nonpropagated potentials are caused by subthreshold.

A) Electrotonus Passive changes caused by subthreshold galvanic current

Catelectrotonus		Anoelectrotonus
Cathode	Occurs at region of	Anode
Depol. less than 7mV	State of	Hyperpolarization
Increased	Excitability is	Decreased

B) Local response (local excitatory state)

Slight active changes which open some Na^+ channels

(5)

Action potential	Local response
Threshold or suprath. stimuli	Subthreshold stimuli
Propagated	Localised (non propagated)
All or none law can't be graded	No all or none law Graded
ARP ^{تراثي} can't be summated	No ARP (excitability increases) Summated
All voltage gated Na^+ channels are opened	Some voltage gated Na^+ channels are opened

absolute
refractory
period

Excitability changes during nerve stimulation ^{قريب من firing level والعكس بالعكس}
 1 During cathelectrotonus, local response and initial depol up to firing level, excitability is increased. (during anelectrotonus excitability $\ominus$)

2 <u>Absolute refractory period ARP</u> Excitability is <u>zero</u> No stimulus can excite <u>length</u> <u>ascending limb</u> from $-65mV$ and early part of descending limb <u>Cause</u> Na^+ channels are inactivated	3 <u>Relative refractory period RRP</u> Excitability <u>below normal</u> <u>Stronger</u> stimulus is needed to excite. <u>length</u> <u>Rest of descending limb</u> including hyperpolarization. <u>Cause</u> Some Na^+ channels are still inactivated Some K^+ channels are activated
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Importance of ARP : Necessity of having afferent & efferent fibres
 2 Protection of nerve from extremely rapid repeated stimuli

Factors affecting membrane potential and excitability of the nerve:

Role of Na^+

① $\oplus\oplus$ Na^+ permeability rapid depol. $\oplus\oplus$ -- ionised Ca^{++} in ECF veratrine	<u>Effect</u> <u>Excitability</u> e.g	$\ominus\ominus$ Na^+ permeability n. impulse fails to produce $\ominus\ominus$ membrane stabilizers $\oplus\oplus$ ionised Ca^{++} in ECF fluid Local anesthetic e.g cocaine
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$K \Rightarrow$ Polarized state

[2] Hyponatremia i.e. $-- Na^+$ in ECF $\rightarrow$ $--$ size (amplitude) of action potential but it has little effect on RMP

[3] Blockage of Na^+ channels by tetrodotoxin (TTX) $\rightarrow$ decreased nerve excitability and no A.Potential is elicited (produced).

[B] Role of K^+

Polarized state (RMP) is primarily dependent on Potassium conc. gradient. Repolarization is caused by Potassium exit

[1] $--$ extracell. K^+ conc. $\rightarrow E_K$ is more $(-ve)$ i.e. hyperpolarization
This occurs in familial periodic paralysis; a hereditary disease treated by IV administration of K^+

[2] Hyperkalemia $\rightarrow E_K$ is more $(+ve)$ i.e. depol $\rightarrow$ $(++)$ excitability

[3] Blockage of K^+ channels by tetraethylammonium (TEA) leads to AP of longer duration due to prolonged repol. but no hyperpolar.

[C] Role of Na^+-K^+ pump Only prolonged blockage of Na^+-K^+ pump will affect RMP (more +ve) i.e. depol and will affect A.potential.

N.B Accommodation of nerve fibre is explained by:

Slow activation opening of Na^+ channels (slow entry of Na^+) is balanced by:
1. Inactivation (closure) of Na^+ channels. 2. Opening of K^+ channels.

Conduction propagation of action potential

[1] Propagation in Unmyelinated axons

AP generated acts as a stimulus for production of AP on adjacent region

- During reversal of polarity (overshoot) of AP a potential difference is generated between the stimulated area and adjacent (resting) area.
- Local circuit occurs between " " and " " (resting) area i.e. +ve charges flow passively to the area of negativity on both outer and inner surfaces of mem. and across the membrane to close the circuit. and complete a closed loop of current flow. This results in: (7)

- 1 Adjacent resting area become depol & the entire process is repeated
- 2 Active segment returns to its resting level.

N.B Original AP is not propagated but generates identical AP in adjacent area
The speed of propagation $\propto \sqrt{\text{Fibre diameter}}$.

B Propagation in myelinated axons Saltatory conduction.

The same principle of unmyelinated axons.

AP is generated only at nodes of Ranvier where voltage gated Na^+ chann. exist

One node becomes the stimulus for generation of AP in adjacent nodes.

The +ve charges have to JUMP from resting to active node (saltatory cond)

Speed of propagation $\propto$ internodal distance and $\sqrt{\text{diameter of fibre}}$

In general, as the diameter increases, the internodal distance increases.

Importance (advantages) of saltatory conduction.

- 1 It ++ velocity of n. impulse conduction up to 50 folds.
- 2 It consumes less energy, as reestablishment of Na^+ & K^+ concentration by Na^+-K^+ pump is restricted only to the nodes.

N.B Orthodromic conduction In living animals, impulses normally pass in ONE direction i.e from receptor or synapse along axon to its end.

Antidromic conduction is conduction in opposite direction

However, " " Fails to pass the 1st synapse the impulse meets

Nerve Fiber types MCQ

	A α, β, γ	B Fibres	C Fibres
<u>Diameter</u>	2 - 20 μ	1 - 5 μ	< 1 μ
<u>Velocity</u>	20 - 120 m/s	5 - 15 m/s	0.5 - 2 m/s
<u>Spike duration</u>	0.5 msec	1 msec	2 msec
<u>e.g</u>	Somatic fibres	Pregang aut.	Postgang aut.
<u>Most sensitive</u>	Pressure	Hypoxia	Local anesthetic

N.B Neurotrophins + pls necessary for neuronal growth, development & survival
Secreted by glial cells, muscles and other structure.

They are internalised & transported retrograde to neuronal cell body.
Metabolism of nerve

- RMP & AP : Energy needed for $\text{Na}^+ - \text{K}^+$ pump

Pump activity $\propto (\text{Na}^+ \text{ conc. inside the membrane})^3$

i.e if Na^+ conc. is doubled, activity is increased $(2)^3$ i.e 8 folds

- During activity heat production is increased in 2 phases:

a Initial heat : during A.P.

b Recovery heat : After A.P. 30 times the initial heat.

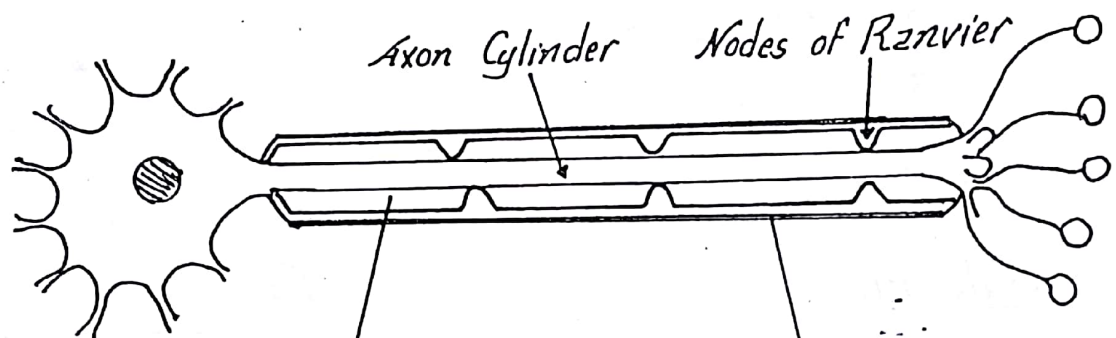
energy

$\uparrow \text{Na}^+$
inside

→ need energy to outflow

NERVE

Neurone Structural unit of nervous system

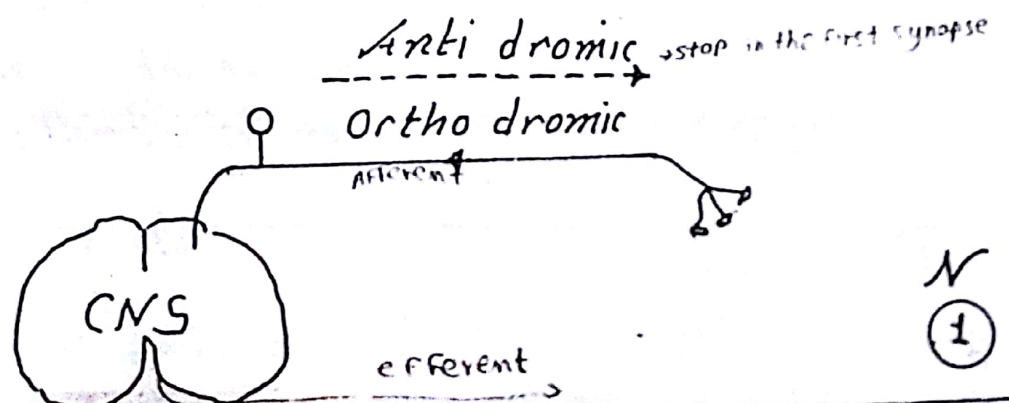


Myelin sheath
rapid conduction
some nerves A & B
Formed by Schwann cells

Neurolemmal sheath
regeneration
all nerves

Types of nerve fibres

100	10	1 meter/second
		has schwann cells
		less than 1μ
↑ <u>Myelinated</u>	↑	<u>Unmyelinated</u>
e.g. <u>Somatic</u>	<u>Pregang. autonomic</u>	<u>Postganglionic autonomic</u>



Excitability

= power to respond to an adequate stimulus.

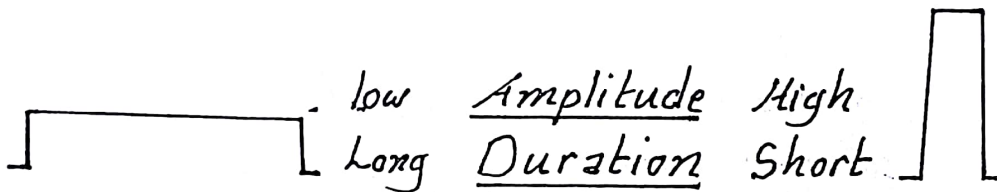
Stimulus

= Sudden change in the environment.

- 1 Mechanical . 
- 2 Chemical . 
- 3 Thermal . 
- 4 Electrical . 

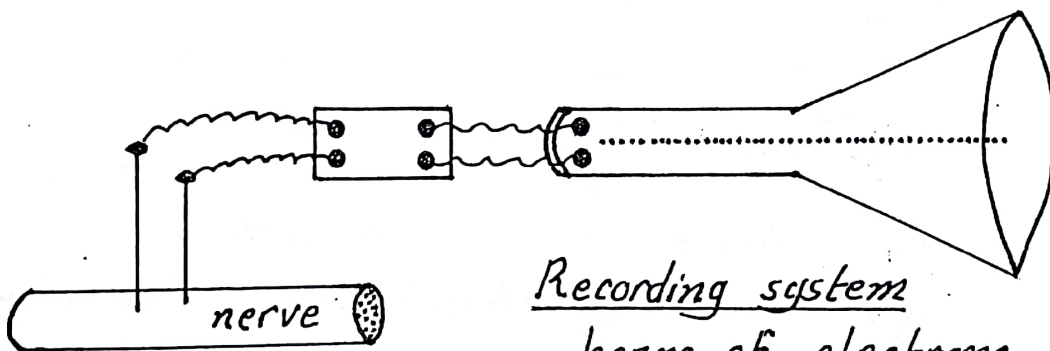
Galvanic

Faradic



Excitability is an electrical phenomenon.

It is measured by CRO ^{"special galvanometer"}
Cathode Ray Oscilloscope.



Recording system

beam of electrons N
no weight no inertia (2)
can follow small & rapid changes

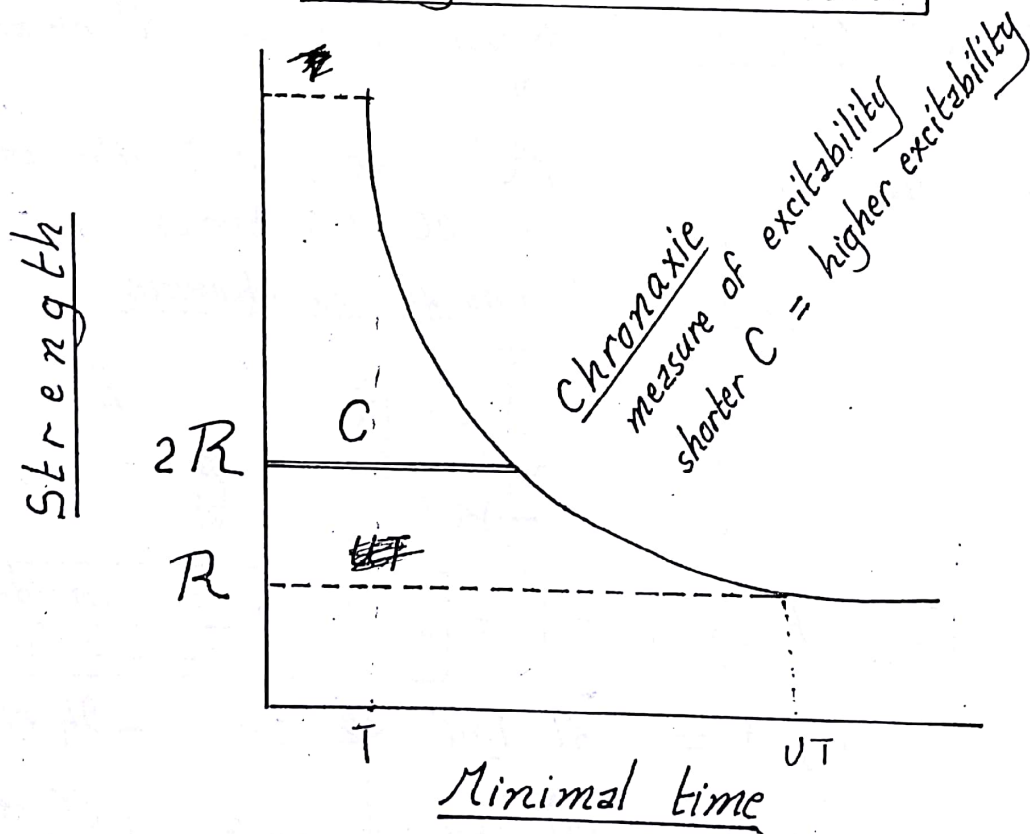
Effectiveness of a stimulus

① Rate of application.

Subthreshold $\xrightarrow{\text{slow increase in intensity}}$ Accommodation
stimulus

② Strength
③ Duration $\rightarrow$ Strength-Duration curve

Strength-Duration curve



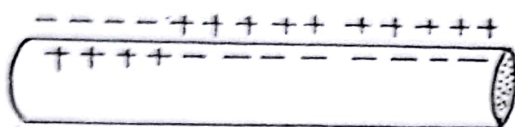
UT utilization time minimal time needed by R
 T minimal time
 C chronaxie minimal time needed by $2R$.
 R rheobase minimal current

③

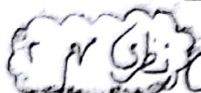
Polarized state

= Resting Membrane Potential RMP

i.e Potential of membrane during rest



$A \propto -90 \text{ mV}$
medium -70 mV



Causes of RMP

①

Selective permeability

Passive

Contributes to -86 mV

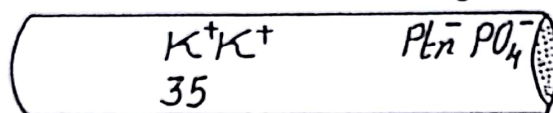
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Ions

$10 \text{ } Na^+ Na^+$

$Cl^- HCO_3^-$

$P_{K^+} \propto \text{Protein} \propto \text{pH}$



•

Channels

Inwards rectifier K^+ channels

(Na^+ & K^+)

P_{tn}

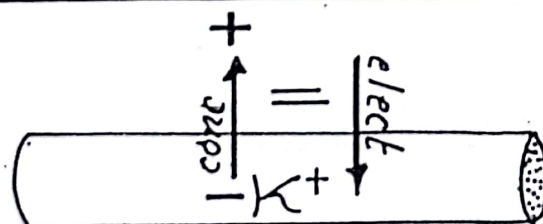
$K^+ > Na^+, Ca^{++}$ & other ions

K^+ & Na^+ leak channels

$K^+ \text{ } P_{K^+} \propto \text{Protein} \propto \text{pH}$

20 - 100 times

Movement of ions across channels



E

Nernst equation

$$= -61 \log \frac{\text{conc. inside}}{\text{conc. outside}}$$

$$E_{K^+} = -61 \log \frac{35}{1} = -94 \text{ mV}$$

$$E_{Na^+} = -61 \log \frac{1}{10} = +60 \text{ mV}$$

Goldman equation

All ions
Permeability

-86 mV

④

②

Sodium - Potassium Pump

Active

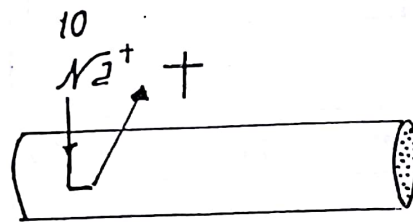
Contributes - 4 mV

● Sodium pump:

Against

- Concent. gradient

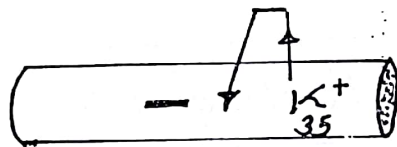
- Electrical gradient



● Potassium pump:

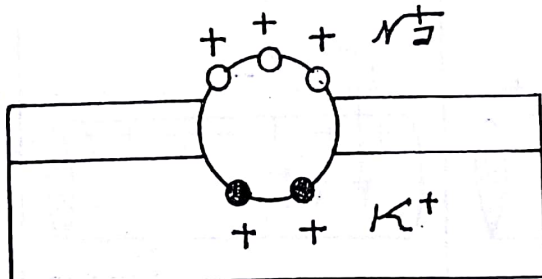
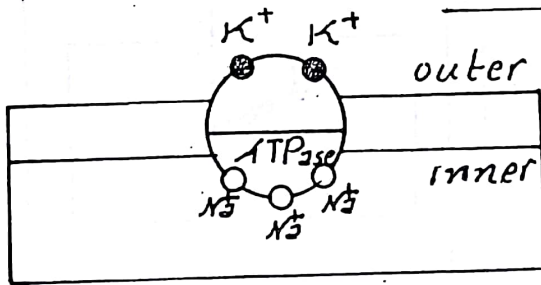
Against

- Concent. gradient



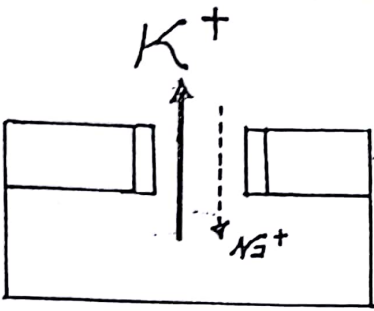
● Mechanism of Sodium-Potassium pump:
Electrogenic pump

All sites are saturated
ATPase is activated

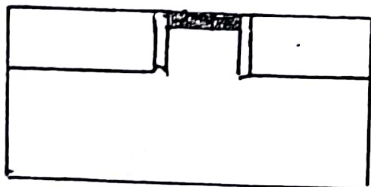
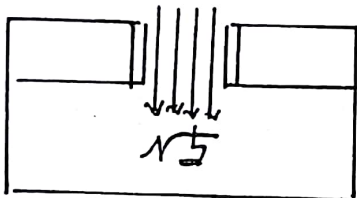
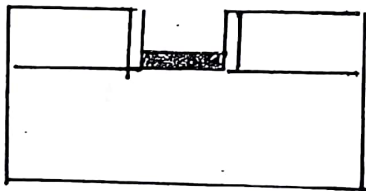


Functions:

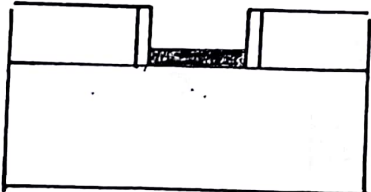
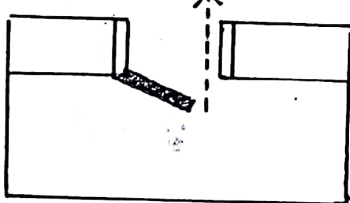
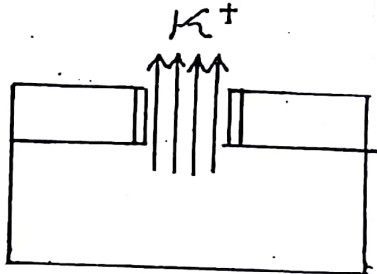
- 1 It keeps Na^+ outside and K^+ inside
- 2 RMP It creates potential difference
outer surface (more +ve) ⑤

Polarised state	Depolarization	Repolarization
	<u>Reversal of polarity</u>	

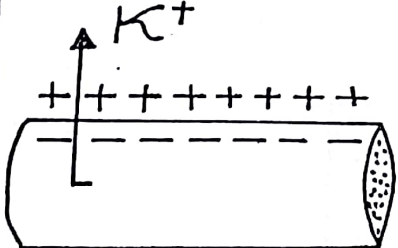
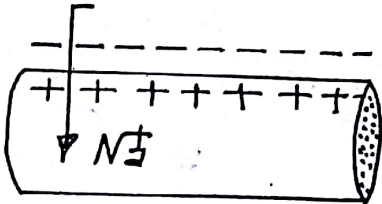
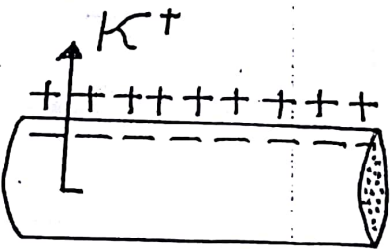
Inwards rectifier potassium channels

 Resting state	Rapid  Activated channel	 Inactivated channels
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Voltage gated sodium channels

	Slow K^+ 	
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Voltage gated potassium channels

 - 90 mV	 + 35 mV	 - 90 mV
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⑥

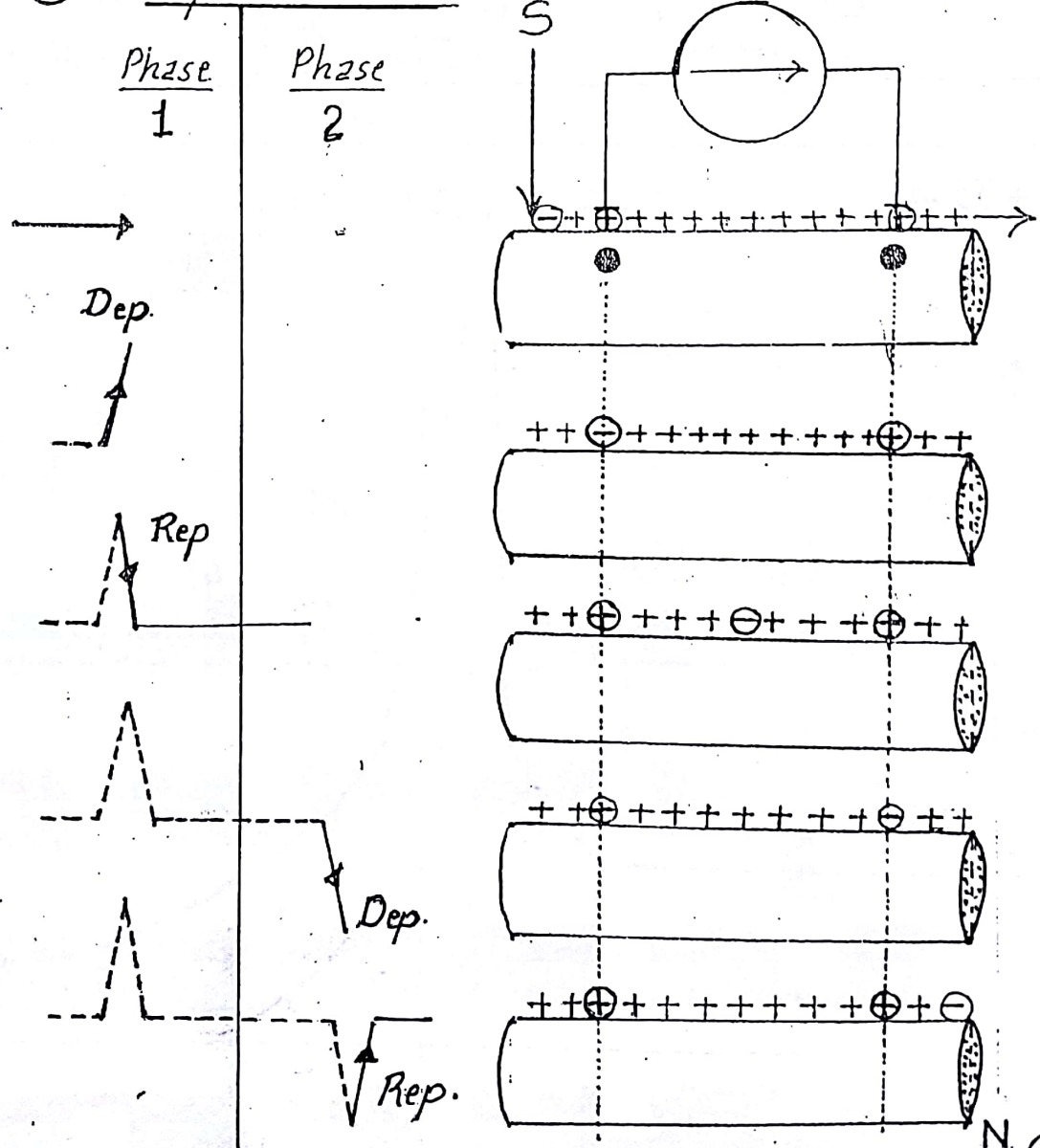
Action potential

nerve impulse
nerve signal

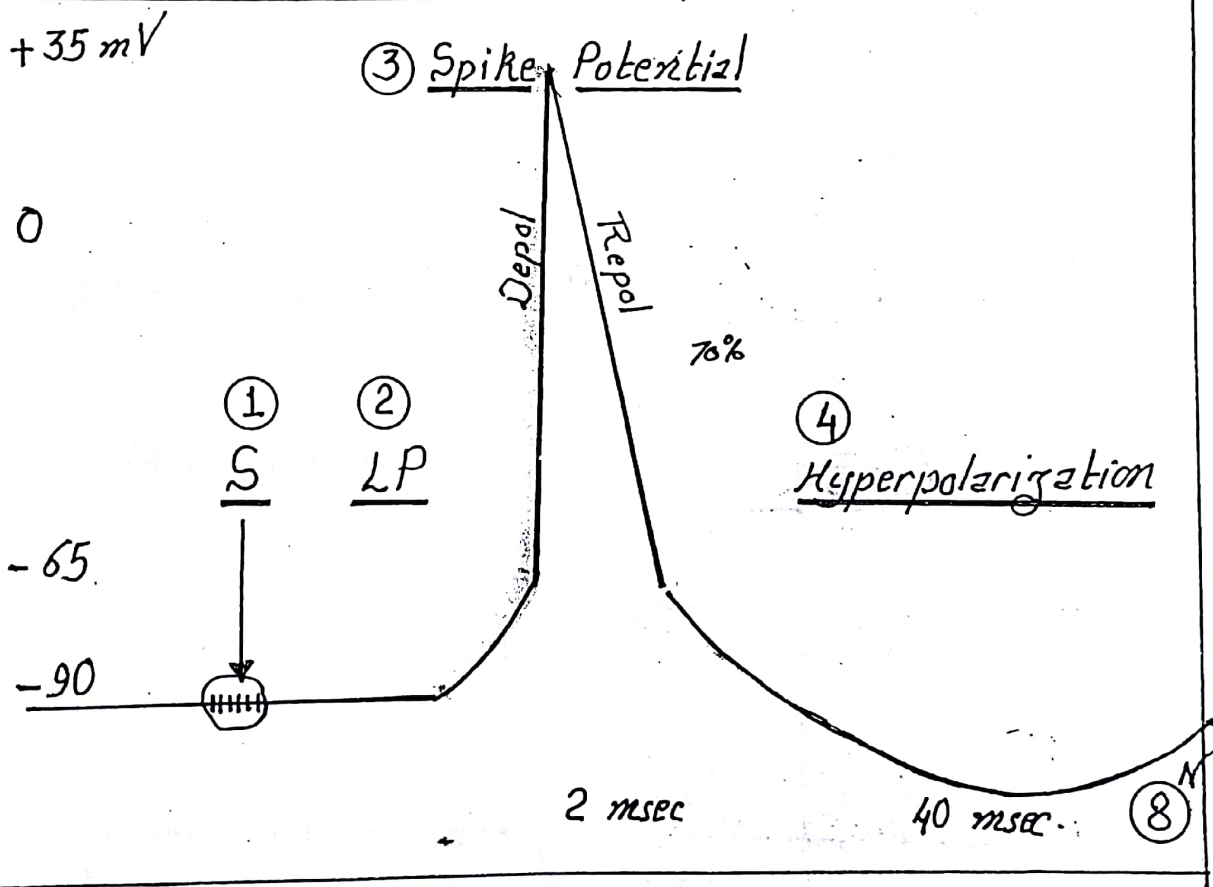
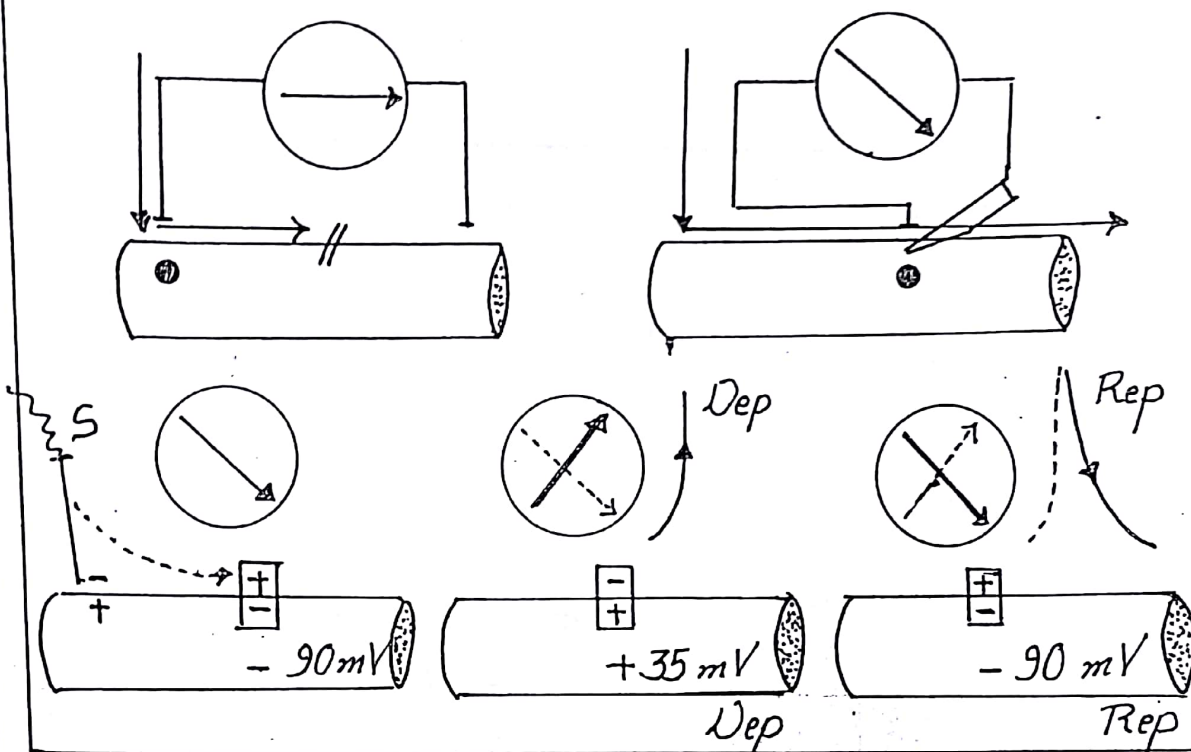
Definition : Depol.
+ Repol.

Types :

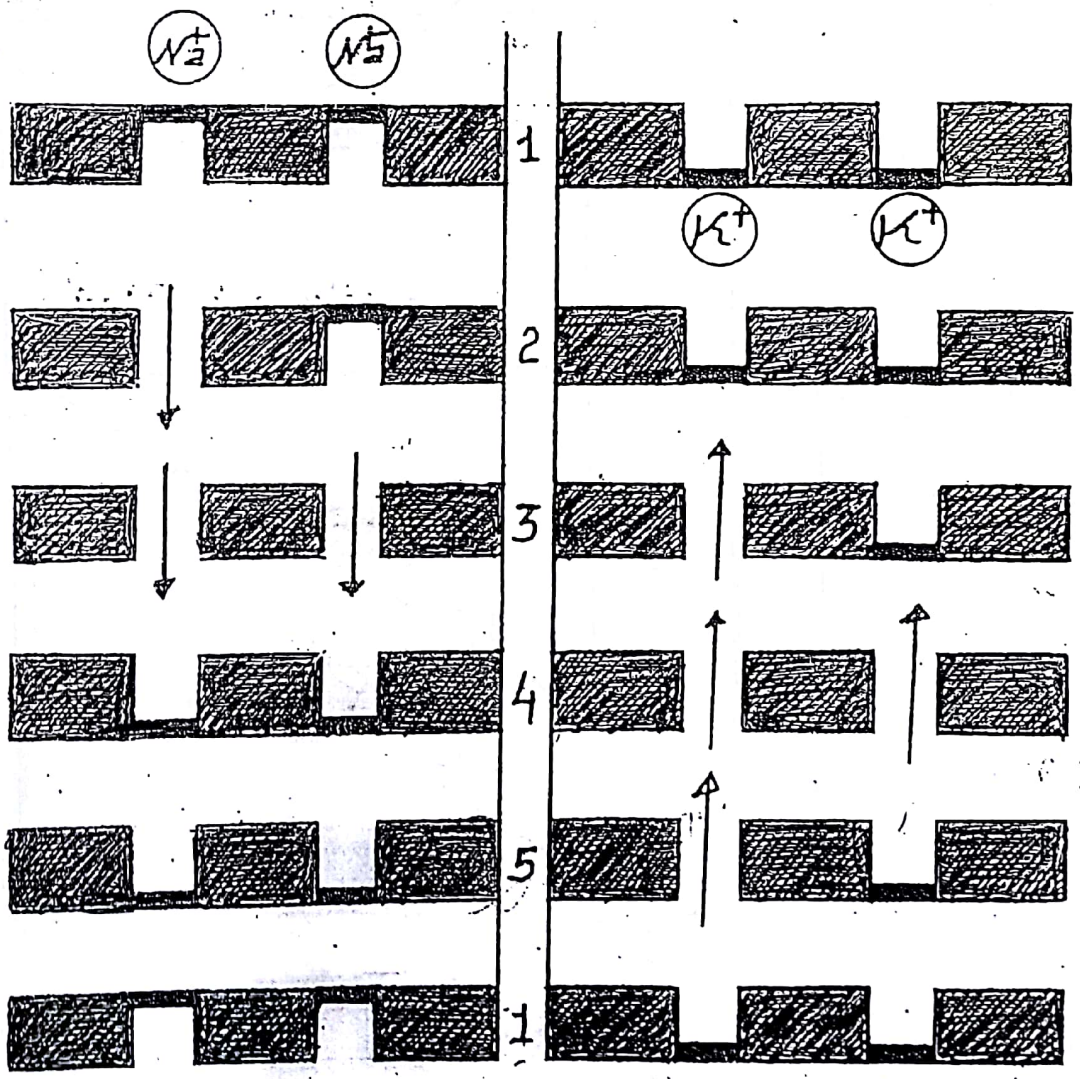
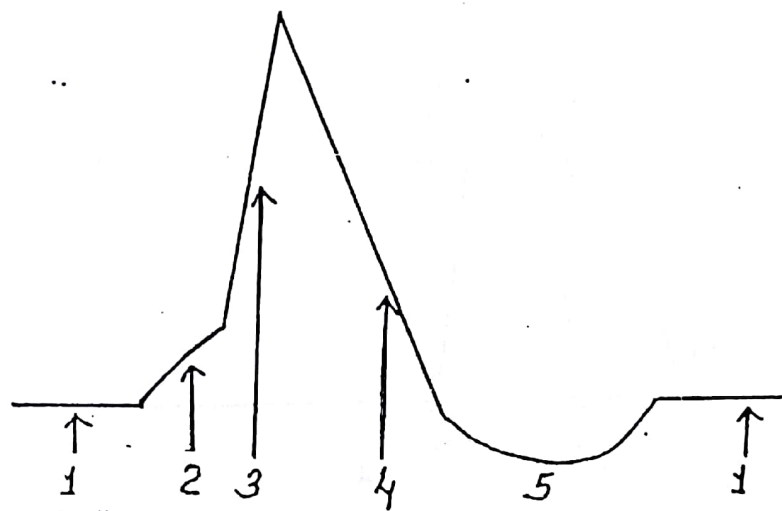
① Biphasic AP



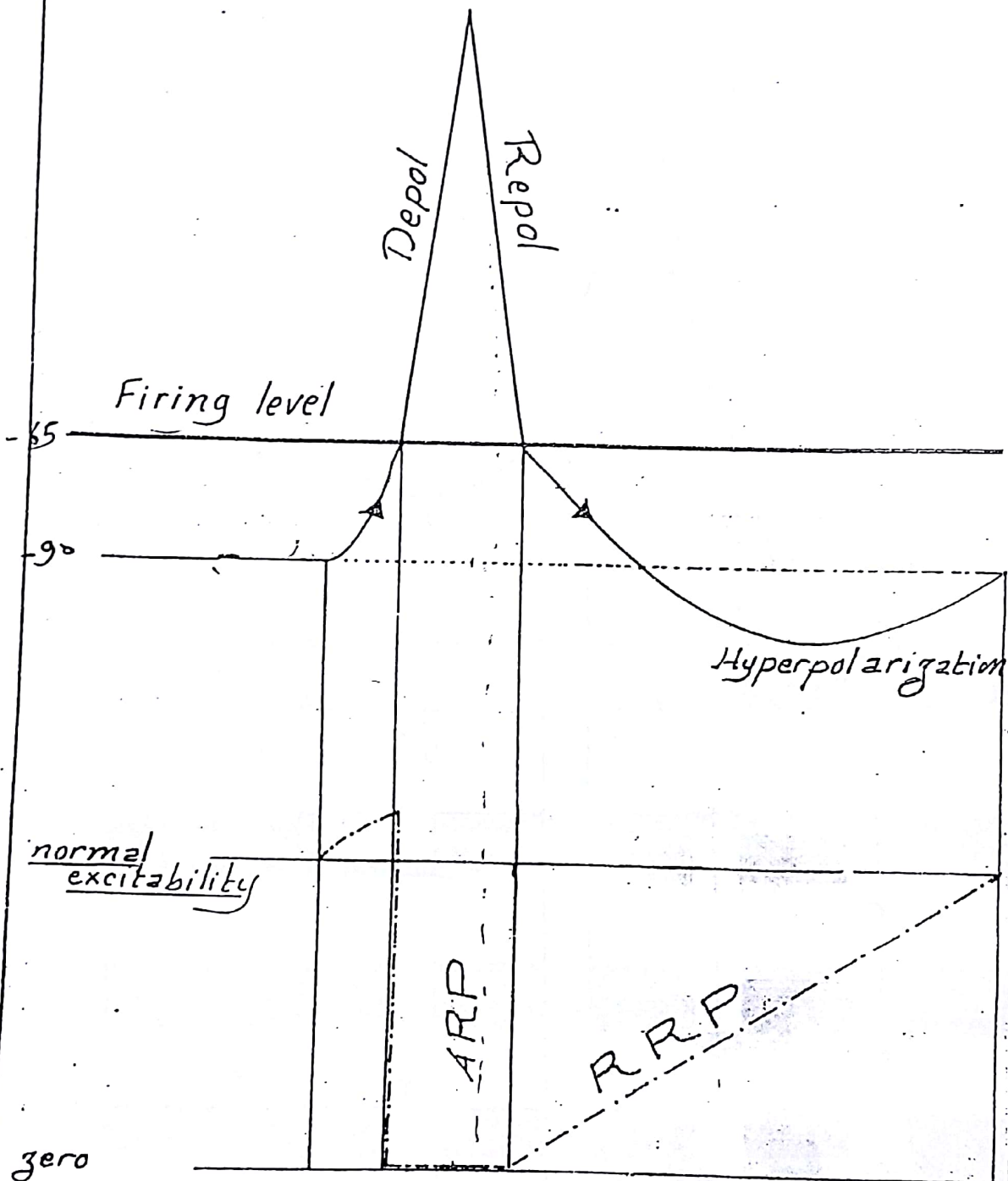
Monophasic Action Potential

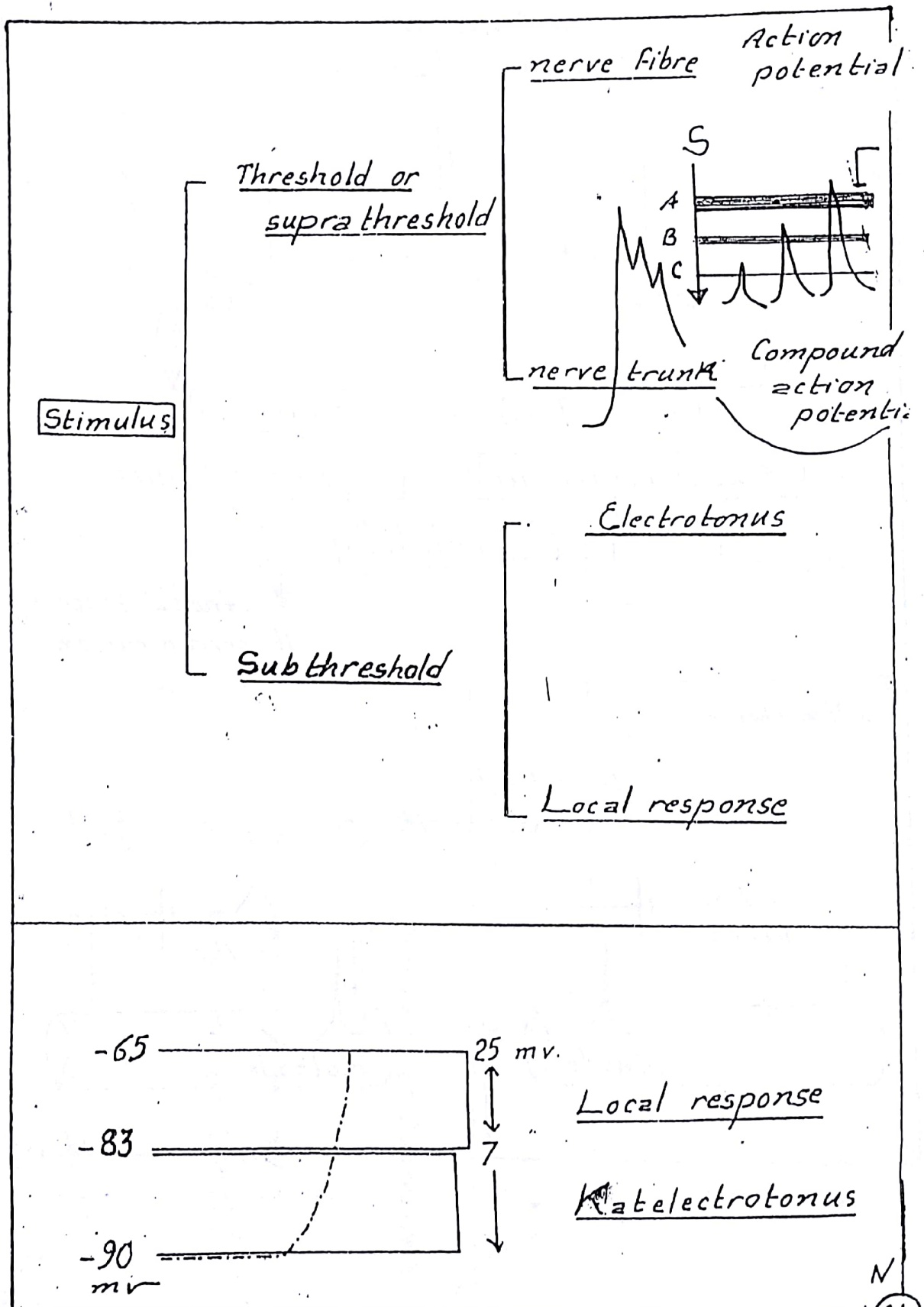


Ionic basis of action potential



Excitability Changes During A. potential





Electrotonus

نقل

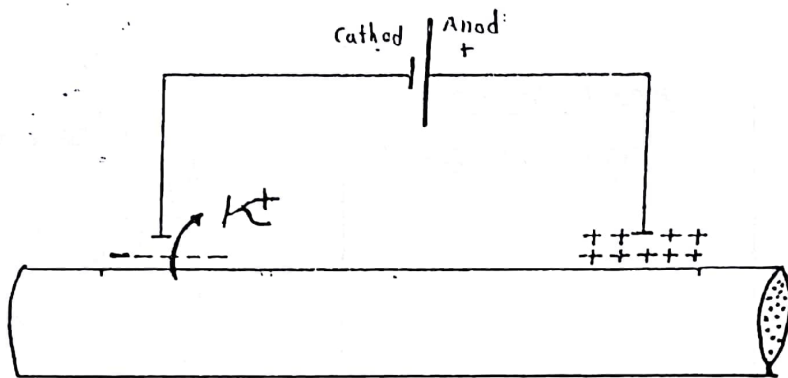
جهد

Subthreshold



Galvanic

Passive changes



Depol. < 7 mV

Hyperpol.

K+ electrotonus

Anelectrotonus

Excitability

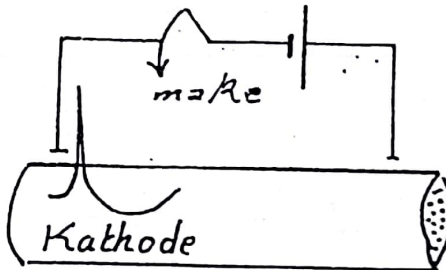
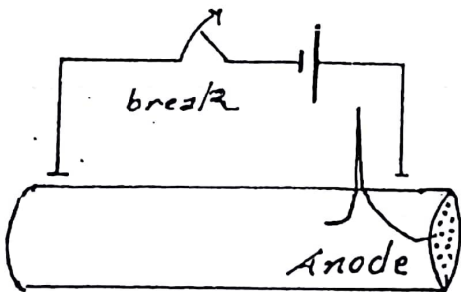
Anodal block if strong current

* ملاحظة عند إنشاء التيار المستمر

Sudden change

المرور المستمر ليس بتغيير

Threshold Galvanic



Local response

Local excitatory state



- ① Subthreshold
- ② Localised (non propagated)

- ③ Does not obey all or none law
- ④ Can be graded

- ⑤ No ARP
- ⑥ Can be summated

i.e. Excitability is increased

So it might reach action potential

Action potential

All or none law

ARP
Anesthesia blocks
الحساسية
All Not characteristic



- ① Threshold or suprathreshold
- ② Propagated

- ③ All or none law
- ④ Can't be graded

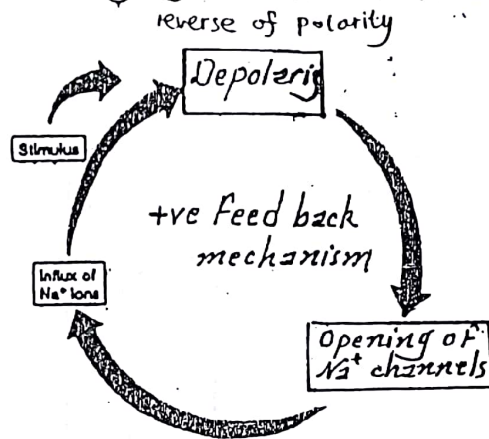
- ⑤ ARP
- ⑥ Can't be summated

N 13

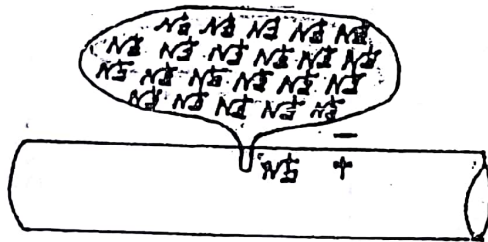
فك كيف تتركز الاستجابة في مكان محدد

من عدة محاور الاستجابة

Opening of voltage gated Na^+ channels



At firing level, all voltage gated Na^+ channels are opened.



Reversal of
polarity not conc.

انعكاس استقطاب وليس انعكاس تركيز

MCQ

Depolarization	Opened Na^+ channels	Membrane
Apot. (firing level)	All	slightly active
Local response	Some	slightly active
Katelectrotonus	No	Passive (inactive)

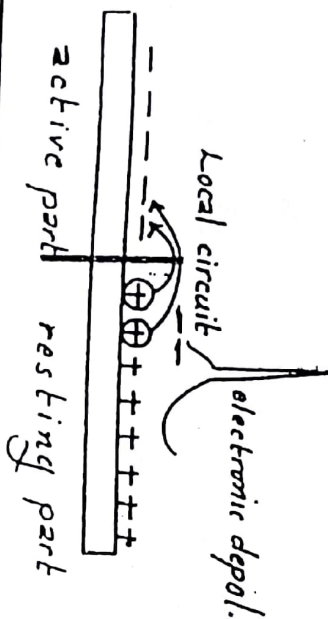
N.B. Electrotonus is caused by the electrical stimulus "S"

Anelectrotonus
Hyperpolarisation $\propto S$

Katelectrotonus
Depol. is not $\propto S$
as depol opens Na^+ channels
→ greater response (14) N

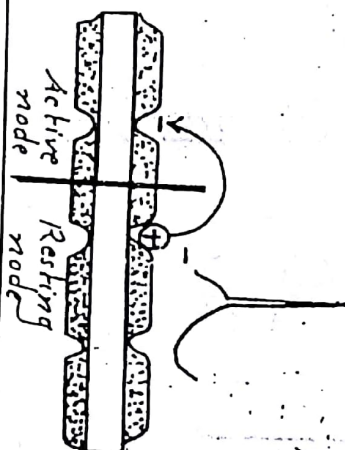
Conduction (Propagation) of A. Potential

Unmyelinated



- resting part : Polarised state
- active part : Depolarised
- local circuit : i.e. electronic depol.
- resting part : Depolarised when depol reaches the firing level $\rightarrow$ action potential ≈ 50 m.

Myelinated



- Saltatory conduction
1. More rapid
Depol jumps long intervals along axon
50-100 times more rapid
 2. Less energy
 $Na^+ - K^+$ pump which restores ionic comp. is restricted to nodes of Ranvier.

Types of nerve fibres :-

thick Myelinated thin		Unmyelinated
<u>A</u>	1-20 μ 100 m/sec.	<u>C</u> < 1 1 m/s
<u>somatic</u>	<u>pregang</u>	<u>post gang</u>
<u>sensitive</u> Pressure	Hypoxia	Local anaesthetics e.g. cocaine